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Current Opinion in Virology

An animal model that reflects human disease: the common marmoset (*Callithrix jacchus*)

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The common marmoset is a new world primate belonging to the Callitrichidae family weighing between 350 and 400 g. The marmoset has been shown to be an outstanding model for studying aging, reproduction, neuroscience, toxicology, and infectious disease. With regard to their susceptibility to infectious agents, they are exquisite NHP models for viral, protozoan and bacterial agents, as well as prions. The marmoset provides the advantages of a small animal model in high containment coupled with the immunological repertoire of a nonhuman primate and susceptibility to wild type, non-adapted viruses.

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Current Opinion in Virology 2012, **2**:357–362

This review comes from a themed issue on
Vaccines
Edited by Connie Schmaljohn and Christian Mandl

Available online 14th March 2012

1879-6257/$ – see front matter

DOI 10.1016/j.coviro.2012.02.007

Introduction

The common marmoset is a new world primate belonging to the Callitrichidae family. The animals are native to the Atlantic coastal forests in northeastern Brazil, but the supply for research comes from National Primate Research Centers, pharmaceutical companies, and breeding facilities [1]. It is small in size with adults weighing 350–400 g. The lifespan of marmosets is relatively compact compared to other nonhuman primates (NHPs), with animals reaching maturity by 18–24 months of age, producing offspring by three years of age and reaching old age by 8 years of age [2]. The compressed lifespan of the marmoset is attractive in scientific research because the number of marmosets available for research can be scaled up quickly when the need arises and then naturally reduced when large numbers of animals are not needed [1,3••].

The marmoset has been shown to be an outstanding model for studying aging, reproduction, neuroscience, toxicology, and infectious disease [3••]. With regard to their susceptibility to infectious agent, they are exquisite NHP models for viral, protozoan and bacterial agents, as well as prions [3••,4,5•,6,7•,8,9•,10,11•,12]. That they do not carry herpes b virus (*Macacine herpesvirus 1*), unlike macaques, which harbor the virus, is an especially desirable trait for those who handle the monkeys [3••]. For the purposes of this review, the focus is on the use of marmosets in high biocontainment, highlighting how they reflect human disease.

Marmoset as a small animal model for hemorrhagic fever

Hemorrhagic fever is an often-fatal disease caused by RNA viruses belonging primarily to bunyaviridae, arenaviridae and filoviridae families. Because of the high morbidity they induce and the lack of approved vaccines and therapies, many of these viruses can only be handled safely using Biosafety level 4 practices. Disease severity, imported cases of disease from patients that traveled to endemic areas, and the potential use of this agent as a biological weapon underscore the need to understand its viral pathogenesis as well as to develop intervention strategies [13–16]. The unique characteristics of the marmoset make it especially suited for high biocontainment research. In particular, the small size of the animal as opposed to larger NHP species makes husbandry less cumbersome and time-consuming thus using these monkeys at high containment is safer and less expensive than using larger NHP counterparts. In addition, current small animal models for some hemorrhagic fever diseases require the use of rodent-adapted viruses, which have been shown not to be especially predictive of efficacy in NHPs. The marmoset has the advantage that it is susceptible to infection with wild-type viruses, which is desirable for testing vaccines and therapeutics.

Arenavirus induced hemorrhagic fever

Lassa fever

Lassa virus, a member of the Arenaviridae family, is the causative agent of Lassa fever. The fatal disease affects more than 300 000 people a year in western Africa and has an overall instance of fatality of 1–2%. The virus is transmitted from a natural rodent reservoir to humans via contaminated rodent excreta or by close contact with infected individuals [13]. Following an incubation period of 7–18 days, the disease is marked by a gradual onset of symptoms including fever, weakness and malaise. As the disease progresses, nausea, vomiting, diarrhea and abdominal pain are often observed. Hemorrhage on mucosal surfaces, such as conjunctival hemorrhages or gastrointestinal or vaginal bleeding, occurs in less than

20% of the cases. Late stages of the disease are marked by shock, seizures and coma, culminating in death [13].

It has been demonstrated that a single subcutaneous inoculation of common marmosets with Lassa virus resulted in a systemic viral disease with fatal outcome and histological features similar to those described in fatal disease in humans [7•]. The experimental infection resulted in a systemic viral disease with high viremia, elevated liver enzymes and decreased levels of albumin in plasma; weight loss; and severe morbidity 15–20 days after inoculation. Histological analysis of tissue from infected animals identified lesions comparable to those described in human cases of fatal Lassa fever, and included hepatic and adrenal necrosis, lymphoid depletion, and interstitial nephritis [7•,10]. The model also demonstrated that the virus induces alterations in target tissues that would be expected to impair adaptive immune responses [7•] consistent with the observations of immunosuppression contributing to Lassa disease progression in humans [17].

In fatal Lassa fever cases and Lassa virus-infected experimental animals the liver is one of the most affected organs participating in a systemic breakdown [18–20]. The most prominent morphological features of Lassa virus-inducible hepatitis in common marmosets were: (i) multifocal hepatic necrosis with mild inflammation presented predominantly by HAM56-positive macrophages; (ii) near absence of CD20-positive, CD8-positive, or CD3-positive lymphocytes in necrotic foci; (iv) the complete lack of expression of MHC-II antigen; and (v) hepatocyte proliferation as judged by positive Ki67 staining. These findings suggest evasion of the normal immune response as a virulence factor in the development of Lassa virus-induced hepatitis [7•].

Lymphoid depletion, a major finding in humans, was also observed in the spleen and lymph nodes of Lassa virus-infected marmosets. These changes were most pronounced in lymph nodes marked by loss of follicles and infiltration by large numbers of histiocytes. In addition to liver tissues, a marked reduction in the intensity of HLA-DR staining was also observed in lymph nodes in Lassa virus-infected marmosets. Alterations in the spleen included reduction in overall numbers of CD3-positive and CD20-positive lymphocytes in Lassa-infected marmosets [7•]. The immunosuppressive phenotype of Lassa virus infection was previously based on detection of proinflammatory cytokines and immunomodulatory molecules in culture medium of human cells infected *in vitro* [21–24], in plasma of experimentally infected animals [25], or in Lassa fever patients [17].

Argentine hemorrhagic fever

Junin virus is the causative agent of Argentine hemorrhagic fever, for which no licensed vaccine or specific antiviral exists in the United States [26]. Humans become infected by inhalation of aerosolized rodent excrement or blood or direct contact with infected animals. The mortality rate for the disease is 15–30%. Early clinical symptoms of infection include fever, fatigue, nausea, and mild hemorrhaging (petechiae), usually in skin or mucosal tissues [27,28]. The initial targets, such as macrophages, recruit additional sentinel cells, through the secretion of cytokines and chemokines, leading to disseminated viral infection. Disseminated infection leads to lack of immune control, increased endothelial leakage and platelet defects.

Common marmosets were successfully used for pathogenesis and protection studies with Junin virus [29–33]. Infection of *Callithrix jacchus* with the prototype strain of Junin virus produced a fatal disease with multifocal hemorrhages and characteristic microscopic lesions such as meningoencephalitis, lymphocytic depletion of lymphatic tissue, hepatocytic necrosis, interstitial pneumonia, and a variable decrease in bone marrow cellularity [29]. High virus concentrations correlated with lesions and with the presence of virus antigen [29].

Filovirus induced hemorrhagic fever

The family Filoviridae predominantly consists of two genera – Ebolavirus (EBOV) and Marburgvirus (MARV). The genera EBOV comprises five species: the prototype, Zaire; Sudan; Bundibugyo; Taï Forest (the virus formerly known as 'Ivory Coast'); and Reston. EBOV Zaire, Sudan and Bundibugyo, as well as MARV, are responsible for sporadic, highly lethal outbreaks of severe hemorrhagic fever in both humans and apes in sub-Saharan Africa, with mortality rates sometimes approaching 90% [34]. Although the primary animal host for the filoviruses is still somewhat unclear, as with other tropical viral diseases, bats have been strongly implicated as a possible reservoir [35,36]. However, the description of EBOV Reston in pigs in Asia [37] serves as a warning about the potential ease with which these viruses may arise and spread in diverse species and populations. No FDA-approved vaccines or specific treatments are currently available for filoviruses, although recent advances in vaccine development are promising.

The common marmoset is susceptible to experimental infection with viruses from the family Filoviridae [9•]. The intramuscular inoculation of as little as 10 PFU of either EBOV or MARV induced pathological features similar to those observed in human disease. Most notably, animals experienced thrombocytopenia, neutrophilia and disseminated intravascular coagulation [9•]. Marmosets had high virus loads in blood and tissue regardless of dose of virus or agent. Furthermore, the small NHP experienced a disease syndrome comparable to what has been reported in other NHP models currently used to study filovirus disease.

Inoculation of marmosets with Zaire ebolavirus resulted in an acute disease. Marmosets experienced anorexia coinciding with the onset of fever. Shortly after these initial findings, anorexia and varying degrees of recumbency were observed, culminating in prostration and death at 4–5 days post-challenge [9•]. Previous work has shown that intramuscular inoculation of macaques with MARV results in a similar course of disease; however, overall disease progression was delayed [38–40]. Experimental inoculation of marmosets with MARV also results in delayed onset of disease, with death occurring 3–4 days later than seen with marmosets infected with EBOV. However, the course of Marburg disease in marmosets was more rapid than that seen in macaques, with death occurring several days sooner than in macaques [9•].

Marmosets infected with either of the filoviruses display neutrophilia, lymphopenia and thrombocytopenia. These hematological abnormalities are also seen in human infection [41,42,43•]. Shortly after infection, overall platelet counts decreased while neutrophil numbers increased, with a concomitant decrease in lymphocyte numbers. In addition, infected marmosets showed biochemical signs of liver involvement early in infection with elevated markers of liver function (ALT, ALP, GGT). Gross examination of the liver revealed hepatomegaly with pale foci throughout all lobes while microscopic examination of sections from the liver revealed necrosis with mild to moderate inflammation [9]. Similar findings have been documented in the macaque model of filovirus infection and in fatal human cases [43•,44,45].

Fatal human cases are characterized by hemorrhage and bleeding at site of venipuncture and other coagulation abnormalities. The coagulopathy observed in humans at times exists in the absence of rash: only 50% of patients infected with EBOV develop a maculopapular rash [47]. Marmosets do not develop a petechial rash when infected with either MARV or EBOV and in this respect appear to be more similar to the African green monkey model of filovirus infection [38,46]. Further evidence that the marmoset mimics human disease is that microscopic examination of tissue from EBOV-infected animals showed widespread fibrin deposition that is a hallmark of coagulation abnormalities [40,45,48]. EBOV infection of the marmoset caused a severe disseminated viral infection characterized principally by microthrombosis in multiple organs (disseminated intravasculature coagulation). MARV-infected animals displayed moderate fibrin deposition in the spleen. These findings are similar to those seen in human infection and in the macaque [40,43•,45,48]. Interestingly, signs of coagulopathy characteristic of primate infections are observed variably in rodent models [38,49,50].

Marmoset as a model for encephalitis

Eastern Equine Encephalitis (EEE) is an arthropod borne viral encephalitis endemic in North America along the United States Atlantic Coast affecting humans and equines. Severe cases of human infection begin with fever, chills, headache, and vomiting and then rapidly progress to disorientation, seizure and coma owing to encephalitis. EEEV causes greater than 30% mortality and there is no specific treatment. Because alphaviruses are highly infectious by aerosol route, development of countermeasures is of high priority.

Intranasal exposure to a North American strain of EEEV caused lethal encephalitis in marmosets [6]. A decrease in leukocytes was observed in NA EEEV-infected marmosets within 24–48 h of infection, followed by marked leukocytosis before death or euthanasia. Similar to human cases [51], leukocytosis in the marmosets was composed of a mixture of lymphocytes and granulocytes.

The pathological lesions in the CNS of the NA EEEV-infected marmosets were similar to those described for human cases [51–54], where EEEV causes neuronal loss, neuronophagia, perivascular cuffs, focal and diffuse accumulations of inflammatory cells and leptomeningitis in the CNS. Vascular lesions with breakdown in the structure of the vessel wall and the appearance of thrombi and extravasation of red blood cells have often been noted. Foci of necrosis in the gray and white matter have also been reported in severe EEE cases of the disease. Areas of the CNS most frequently subject to severe lesions include the cerebral cortex, basal ganglia, thalamus, hippocampus, and brainstem. By contrast, lesions in the cerebellum and spinal cord are not common findings in human EEE.

South American EEEV strain BeAr436087 was attenuated in infected marmosets, a finding consistent with data derived from mouse studies. There have been only two reported fatal human encephalitis cases of EEE in South America [55]. Humans are most probably exposed in South America but do not develop apparent infection with EEEV because of poor infectivity and/or a virulence of South American strains [56].

Marmoset as a model for SARS

Severe acute respiratory syndrome (SARS) emerged in 2002 and infected 8000 people, causing death in 11% of the cases [57,58]. Humans infected primarily present with pneumonitis but may also develop hepatic, gastrointestinal, and renal pathology. Older people were more often associated with increased SARS pathogenicity and death resulting from acute respiratory distress syndrome [59,60]. Intratracheal inoculation of marmosets with cell culture supernatant containing SARS-CoV develops disease with features similar to human disease [11•]. Mononuclear cell interstitial pneumonitis, accompanied by multinucleated syncytial cells, edema, and bronchiolitis, was observed in most SARS-infected animals while

Table 1

Disease agents.

Disease	Agent	Route	Main feature
Ebola hemorrhagic fever	Ebola Zaire (Kikwit)	Intramuscular	Viremia, hemorrhage, thrombocytopenia, neutrophilia, increase hepatic enzymes, DIC
Marburg hemorrhagic fever	Marburg (Musoke)	Intramuscular	Viremia, hemorrhage, thrombocytopenia, neutrophilia, increase hepatic enzymes, moderate fibrin deposition
Lassa hemorrhagic fever	Lassa (Josiah)	Subcutaneous	Viremia, elevated liver enzymes, multifocal hepatic necrosis, lymphoid depletion, MHC-II and CD20 lymphocytes suppression
Argentine hemorrhagic fever	Junin (XJ Strain)	Intramuscular	Multifocal hemorrhage, lymphocytic depletion, hepatocellular necrosis, viremia
Eastern Equine Encephalitis	EEE (FL93-939)	Intranasal	Encephalitis, neuronophagia, perivascular cuffing, leptomeningitis
SARS	SARS-CoV (Urbani)	Intratracheal	Viral RNA in pulmonary extracts, interstitial pneumonitis and Bronchiolitis

alveolar macrophages and type-1 pneumocytes appeared to be the site of viral antigen localization. Furthermore, pulmonary tissue extracts obtained at necropsy as well as tracheobronchial lymph node and myocardium had detectable levels of viral RNA. Hepatic inflammation was observed in most animals, predominantly as a multifocal lymphocytic hepatitis accompanied by necrosis of individual hepatocytes [11•]. These findings provide evidence that the marmoset is a relevant NHP to study SARS-CoV pathogenesis.

Conclusions

The marmoset has emerged as a viable NHP model for studying high biocontainment infectious disease agents (Table 1). Advantages of using the marmoset are that they mimic human disease, are small in size, provide a cost savings over larger NHP species, require husbandry techniques that are less time consuming, and have fewer biosafety considerations because they are not known to carry endogenous virus harmful to humans. Marmosets, because they are NHPs, provide distinct advantages over rodent species including an immunological repertoire that more closely resembles humans. As testing of vaccines and therapies to high consequence pathogens advances, more robust animal models to validate countermeasures will be required [61].

Because of the sporadic nature of many high consequence pathogens, the incidence of these agents is not predictable and therefore phase III efficacy trials are not feasible. The US Food and Drug Administration (FDA) declared a new regulation in 2002 as an alternative licensing pathway for pharmaceutical products that target highly lethal pathogens when evaluation in the field is not possible. The 'animal rule' will allow approval provided that satisfactory efficacy data are generated in two animal models. In the case of viral hemorrhagic fever, the marmoset offers advantages over rodent species as an alternative small animal model. With regard to filovirus research, in addition to needing rodent adapted virus, mouse and guinea pig filovirus models have not been good predictors of efficacy in higher species. The marmoset model provides the advantages of a small animal model in high containment coupled with the immunological repertoire of an NHP and susceptibility to wild type, non-adapted viruses. Undoubtedly, increased use of marmoset models will accelerate pre-clinical development of vaccines and therapeutics to high consequence pathogens.

Acknowledgements

We would like to thank Sandra Rios, Maria Messenger and Jennifer Meehan for technical assistance in preparing this manuscript. We would also like to acknowledge a NIH laboratory construction grant (C06 RR12087) and the Southwest National Primate Research Center base grant (P51 482RR013986).

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